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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/602,812	06/23/2000	Mark Sliwkowski	P1467R2	9612

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/602,812	SLIWKOWSKI, M.X.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9,12,13,16-22,24-29,34 and 60-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9,12,13,16,18-22,24-29,34 and 60-63* is/are rejected.

7)☒ Claim(s) *17 and 62* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/26/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed June 2, 2004 is acknowledged.

Claims 1, 2, 4-9, 12, 13, 16-22, 24-29, 34 and 60-63 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

3. A Copy of the signed Information Disclosure Statements (PTO-1449) filed 8/26/2004 is included with this Office action.

Rejections Withdrawn:

4. The rejection of claims 27-29, 34 and 60 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment to the claims.

5. The rejection of claims 1, 2, 4-9, 12, 13, 16-22, 24-26, 61, 62 and 63 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment to the claims.

6. The rejection of claims 1, 2, 7, 12, 13, 16, 17 and 20 under 35 U.S.C. 102(e) as being anticipated by Greene et al., US Patent 5,824,311, published October 20, 1998 (IDS # 8), as evidenced by Jardines et al., Pathobiology, Vol. 61, pages 268-282, 1993 is withdrawn.

7. Claims 1, 2, 4, 7, 16, 17, 20, 24-26, 28, 29, 34, and 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak (U.S. Patent 5,725,856; issued 03/1998; effective filing date 01/1988) and Jardines (supra); in view of Sliwkowsky (Sliwkowsky, M.X. et al, J. Biol. Chem. 269: 14661-14665, 1994; IDS) or Klapper (Klapper, L.N. et al. Oncogene, 14: 2099-2109, 1997; IDS); and further in view of Plowman (U.S. Patent 5,804,396; issued 09/1998; effective filing 10/1994; IDS) or Greene (U.S. Patent 6,417,168; issued 07/2002; effective filing 03/1998; IDS).

Claim Rejections Maintained and New Grounds of Rejection:

8. Claims 1, 2, 4, 8, 7, 12, 13, 16, and 20 under 35 U.S.C. 102(e) as being anticipated by Greene et al., US Patent 5,824,311, published October 20, 1998 (IDS # 8), as evidenced by Brabender (Brabender, J. et al. Clinical Cancer Research, 7(7): 1850-1855, 2001) and also evidenced by Zhang (Zhang, H. et al. Experimental and Molecular Pathology, 67: 15-25, 1999).

The claimed inventions are drawn to methods of treating cancer in a human, wherein the cancer expresses epidermal growth factor receptor (EGFR) and ErbB2, comprising administering an antibody that binds ErbB2 and cross-blocks binding of monoclonal antibody 2C4 (ATCC HB-

12697) to ErbB2. The phrase "cross-blocks binding" is interpreted to mean that the binds to an epitope that is nearby or the same as the epitope that is bound by monoclonal antibody 2C4.

Greene teaches a method of treating a patient, which includes humans, by administering a therapeutically effective amount of an antibody that binds ErbB2. Specifically, Greene teaches that the p185 oncogene (which is the same as ErbB2) has been found active in lung adenocarcinoma, and further provides a method of using monoclonal antibodies which bind to ErbB2 to treat mammalian cancer tumors which express a translation of the neu oncogene on their surfaces (see column 3, line 50-column 5). One monoclonal antibody of Greene that is useful for treating lung cancer is 7.16.4, an antibody that binds to a similar epitope on Her-2 that monoclonal antibody 4D5 binds to (as evidenced by Zhang, see abstract). The specification teaches in Figure 1B, that the 4D5 antibody binds to an epitope of 4D5 that appears to be within the range of the putative epitope of 2C4. Because, "cross-blocking" appears to refer to an assay for determining whether two antibodies share an epitope or bind near to each other, the 4D5 antibody appears to be an antibody that would cross-block binding of the 2C4 antibody to erbB2. Furthermore, it appears that the degree of cross-blocking may be quantified, and the claims do not specify the degree to which an antibody must cross-block the 2C4 antibody. Thus, even a small amount of cross-blocking by an antibody would put the antibody within the scope of the antibodies to be used by the claimed methods. Therefore, absent evidence to the contrary the Greene antibody is one that would cross-block binding of monoclonal antibody 2C4. Additionally, applicant has provided no objective evidence to show that any of the Greene antibodies would not cross-block the 2C4 antibody to any degree. The antibody of Greene et al. is not conjugated to a cytotoxic compound.

While Greene et al. does not explicitly recite that the cancer that is treated expresses or overexpresses EGFR, Brabender teaches that expression of EGFR and Her2-neu mRNA expression is detectable in all non-small cell lung cancer (NSCLC) specimens analyzed, and that in some instances lung cancer may be characterized as overexpressing EGFR (see abstract).

9. Claims 1 and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greene et al., US Patent 5,824,311, published October 20, 1998 (IDS # 8), as evidenced by Brabender (Brabender, J. et al. Clinical Cancer Research, 7(7): 1850-1855, 2001) and also evidenced by Zhang (Zhang, H. et al. Experimental and Molecular Pathology, 67: 15-25, 1999).

Claims 1 and 24-26 may be interpreted as drawn to methods reciting dosages and dosage schedules. However, the ability to establish treatment regimens is well known to those of ordinary skill in the art. Thus, it would have been prima facie obvious to one of ordinary skill in the art to have modified the methods of Greene to include treatment regimens.

10. Claims 1, 2, 4, 7, 16, 20 and 22 under 35 U.S.C. 102(e) as being anticipated by Hudziak, US Patent 5,725,856; issued 03/1998; effective filing date 01/1988), published October 20, 1998 (IDS # 8), as evidenced by Suzuki (Suzuki, T. et al. Oncology, 52(5): 385-391, 1995) and as evidenced by Shackney (Shackney, S.E. et al., Clincal Cancer Research, 4(4): 913-928, 1998).

The claimed inventions are drawn to methods of treating cancer in a human, wherein the cancer expresses epidermal growth factor receptor (EGFR) and ErbB2, comprising administering an antibody that binds ErbB2 and cross-blocks binding of monoclonal antibody 2C4 (ATCC HB-

12697) to ErbB2. The phrase "cross-blocks binding" is interpreted to mean that the binds to an epitope that is nearby or the same as the epitope that is bound by monoclonal antibody 2C4.

Hudziak teaches methods for treating cancers such as breast cancer or gastric cancers, which are cancers that coexpress ErbB2 and EGFR as evidenced by Suzuki (gastric cancer) and by Schackney (breast cancer), comprising administering an anti-Her-2 antibody (anti-erbB2). One anti-erbB2 antibody that is taught by Hudziak is the monoclonal antibody, 4D5, which is an antibody that appears to be one that would cross-block the binding of the 2C4 antibody to erbB2. The specification teaches in Figure 1B, that the 4D5 antibody binds to an epitope of 4D5 that appears to be within the range of the putative epitope of 2C4. Because, "cross-blocking" appears to refer to an assay for determining whether two antibodies share an epitope or bind near to each other, the 4D5 antibody appears to be an antibody that would cross-block binding of the 2C4 antibody to erbB2. Furthermore, it appears that the degree of cross-blocking may be quantified, and the claims do not specify the degree to which an antibody must cross-block the 2C4 antibody. Thus, even a small amount of cross-blocking by an antibody would put the antibody within the scope of the antibodies to be used by the claimed methods. Hudziak teaches methods where the 4D5 antibody is not conjugated to a cytotoxic molecule. Alternatively, Hudziak also appears to teach a method where the 4D5 antibody is conjugated to a cytotoxic drug, because the claims recited that the antibody coats a liposome filled with a cytotoxic drug (see claim 20).

11. Claims 1, 2, 7, 9, 16, 20, 34, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak (U.S. Patent 5,770,195; issued 06/1998; effective filing date 01/1988) and any of Maurer (Marurer, C.S. et al. Human Pathology, 29(8): 771-777, 1998), Suzuki

(supra), Shackney (supra) or Bast (Bast, R.C. et al. Cancer Molecular Biology , 1(2): 87-93, 1994); in view of Klapper (Klapper, L.N. et al. Oncogene, 14: 2099-2109, 1997; IDS).

The claimed inventions may be interpreted to be drawn to methods of treating cancers that coexpress ErbB2 and EGFR, where such cancers may be colon, colorectal or rectal, comprising administering an antibody that cross-blocks binding of the monoclonal 2C4 antibody to erbB2 or comprising administering an antibody that binds erbB2 and that blocks ligand activation more effectively than does rhumab4D5-8. The specification teaches that the 2C4 antibody is an antibody that blocks ligand activation of an erbB receptor more effectively than does rhumab4D5-8, and also that the 2C4 antibody is an antibody that inhibits heterodimerization of erbB2 with other erbB receptors such as EGFR and erbB3.

Hudziak '195 teaches methods of using antibodies that bind erbB2 and that may exert their effect on tumor cells by blocking binding of ligand for the purpose of treating cancers that overexpress erbB2. Hudziak does not appreciate that many cancers that overexpress erbB2 also coexpress EGFR or erbB3. Suzuki teaches that gastric carcinomas coexpress erbB2 and EGFR. Shackney teaches that breast cacners coexpress erbB2 and EGFR and Bast teaches that ovarian cancers coexpress erB2 and EGR. Maurer teaches that colorectal cancers coexpress erbB2 and erbB3 and also to some degree EGFR.

Klapper teaches antibodies that inhibit the binding of NDF and EGF to their direct receptors (erbB3 and EGFR, respectively) and Klapper teaches that there are two potential mechanisms for antibody –induced therapy, one of which is the use of an antibody that blocks heterodimerization of erbB-2 and either erbB3 or EGFR (see abstract; and Table 1, describing class II antibodies.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the methods of Hudziak '195 of treating cancers overexpressing erbB2 with an antibody of Klapper because Hudziak appreciated that one mechanism by which an antibody might be efficacious is to block ligand binding to an erbB receptor and because Klapper provides such antibodies, and because the prior art teaches that many tumors that overexpress erbB2 also coexpress EGFR or erbB3. Although Klapper does not compare the ability of the class II antibodies to block ligand activation of an erbB receptor with the ability of rhumab4D5-8, because of the biological properties described by Klapper, absent evidence to the contrary, it appears that Klapper's antibodies would meet this limitation.

12. Claims 1, 18 19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak (U.S. Patent 5,770,195; issued 06/1998; effective filing date 01/1988) and any of Maurer (Maurer, C.S. et al. Human Pathology, 29(8): 771-777, 1998), Suzuki (supra), Shackney (supra) or Bast (Bast, R.C. et al. Cancer Molecular Biology , 1(2): 87-93, 1994); in view of Klapper (Klapper, L.N. et al. Oncogene, 14: 2099-2109, 1997; IDS) as applied to claim 1 above; and further in view of Grim et al., Am. J. Respir. Cell Mol. Biol., Vol. 15, pages 348-354, September 1996).

The claimed methods are interpreted to be drawn to methods using antibody fragments.

The combination of Hudziak and Jardines is silent on methods of using antibody fragments in methods of treatment. However, Grim et al. teaches a method of treating lung cancer by administering an antibody fragment which binds to ErbB2 (see abstract, and especially pages 350 and 353), thus teaching that the ErbB2 receptor is a therapeutic target in lung cancer

and that antibody fragments may be used for treatment purposes. Therefore it would be *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to treat human lung cancer patients with an ErbB2 antibody, and it would have been prima facie obvious to one of ordinary skill in the art to use fragments of the antibodies of Hudziak in methods of treatment.

13. Claims 61 and 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the specification does not describe the structure of the 2C4 epitope. Therefore, applicant does not appear to be in possession of antibodies that bind to the epitope of 2C4.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is for purposes of the 'written description' inquiry, "*whatever is now claimed*" (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed." (See Vas-Cath at page 1116.)

The claimed inventions are drawn to methods using antibodies that bind to erbB2 and bind to the same epitope as does monoclonal antibody 2C4. The specification provides one antibody, that of monoclonal antibody 2C4 that binds to this epitope, and describes a general region in erbB2 where the epitope may be found and assays for screening for antibodies that bind

at the epitope or near to the epitope. However, the assay does not appear to be able to distinguish between antibodies that bind at the epitope from those that bind near to the epitope. Therefore, in view of the fact that the assay does not provide antibodies that bind only at the epitope of 2C4 and in view of the fact that the description of the epitope is not precise, applicant does not appear to have described a genus of antibodies that bind to the 2C4 epitope.

The skilled artisan cannot envision the detailed chemical structure of the 2C4 epitope or the detailed chemical structure of the feature common to a genus of antibodies that bind to this epiotpe. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of manufacturing or testing the claimed process. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making or testing it. One cannot describe what one has not conceived. See Fides v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112, is severable from its enablement provision. (See page 1115).

14. Claims 17 and 62 are objected to because they appear to be claims of identical scope. Correction is required either by amendment of one of the claims to change the scope or by cancellation. Claim 17 is also objected to for depending from a rejected claim.

15. Claims 27, 34, and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 27, 34 and 60 are indefinite because of the word "substantially". The specification contains no definition of what "substantialy more effectively" means, and therefore the scope of the claims cannot be determined. The examiner acknowledges that the amendment to add the word "substantially" was made in response to a new matter rejection in the previous Office action, and will not reinstate the new matter rejection should the word "substantially" be removed from claims 27, 34 and 60.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1, 2, 4-8, 16-22, 24-27, and 60-63 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 and 22-31 of copending Application No. 09/602,800. Although the conflicting claims are not

identical, they are not patentably distinct from each other because the claims of Application No. 09/602,800 are drawn to methods for treating cancer with an antibody that inhibits ligand activation of an ErbB receptor, and uses the monoclonal antibody 2C4.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In response to applicant's arguments, this rejection is maintained because applicant has not shown that prostate cancer is not a cancer that falls within the scope of cancers that coexpress EGFR and erbB2 or cancers that express but do not overexpress erbB2. It is noted that the provisional rejection is made only over the broad claims and not to those claims that recite specific cancers. Therefore, this rejection is maintained because prostate cancer appears to be a cancer that falls within the scope of the cancers treated in the instant application and because the antibodies appear to be the same as those used in the instant application.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
October 1, 2004

LARRY R. HELMS, PH.D
PRIMARY EXAMINER